Remarks

Claims 1-13 are in this case. Applicant thanks the Examiner for renumbering the claims to account for the two claims numbered as Claim 6 as originally filed. Claims 8, 10 and 11 which depend from claims which have been renumbered have been amended such that the dependency corresponds with the new numbering. An Appendix having the claims as pending is attached for the Examiner's convenience.

Double Patenting

The claims have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over copending application Serial No. 07/690,530, (the grandparent to this case), for which an Appeal Brief was filed December 15, 1993, and over copending application Serial No. 08/254,299, (the parent to this case). When there is an indication of allowance of any claims in any of these cases, the provisional double patenting rejections will be avoided.

Claims 9-11 have been provisionally rejected under 35 U.S.C. Section 101 as claiming the same invention as claimed in Claims 8-10 of copending application Serial No. 08/254,299. Applicant will also avoid this rejection when there is indication of allowance of any of these claims but for this issue.

Sequence Listing

Page 15, line 1 has been amended to include a sequence identifier. Enclosed is a paper copy of the Sequence Listing which has been inserted into the specification and updated in the "general information section" by amendment. Also enclosed is a copy of the Notice to Comply Requirements for Applications Containing Nucleic Acid and/or Amino Acid Sequence Disclosures, and a Declaration including a formal request that the computer readable form of the Sequence Listing submitted in the grandparent application be used to prepare a file for this case and a statement that the paper copy of the enclosed

Sequence Listing is identical to the computer readable form of the Sequence Listing submitted in the grandparent application.

Trademarks

The specification has been amended to capitalize trademarks where they appear, and to include the generic terminology following each trademark where the generic terminology does not already follow the mark in the specification.

Rejections under 35 U.S.C. Section 112, first paragraph

Claims 1-13 have been rejected under 35 U.S.C. Section 112, first paragraph, as containing subject matter not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Specifically, the rejection addresses a number of issues which Applicant understands as follows: the *in vitro* or *in vivo* mouse data does not enable the use of the invention in humans; the *in vivo* mouse data relating to lysis of normal cells does not enable treatment of a disease in mouse; antibody conjugates are not enabled (whether they are human or murine) by animal data; therapies having IL-2 or other cytokines as a ligand are not enabled since then normal T cells or other cells expressing receptors to these cytokines would be blocked and inactivated and the therapy would be further complicated if the target cell population was smaller than the population of normal cells having these receptors; therapies utilizing the α-gal antigen are not enabled because they would be quickly removed from the body before reaching the target cell; therapies depending on endogenous antibodies to α-gal antigens are only enabled in humans and old world monkeys; and, the therapies are not enabled because dosages for either the conjugate or the endogenous antibodies required for a therapeutic effect are not provided. Applicant respectfully traverses these rejections.

A review of the standard to determine enablement

The Section 112, first paragraph, rejections are based on the assertion that the specification does not disclose "how to use" the instant invention. The proper standard for determining if a specification discloses "how to use" the invention is set forth in the new guidelines set forth by the Patent Office for determining utility, referred to herein as "the guidelines". As the guidelines were issued by the Patent Office, Applicant has not enclosed a copy herein. First, Applicant points out that the guidelines are applicable to rejections both for lack of utility under 35 U.S.C. § 101 and for failing to teach "how to use" for *in vivo* therapeutic or pharmacological utility under 35 U.S.C. § 112, first paragraph (see, page 296, left column, lines 30-35 and page 300, right column of the guidelines).

The guidelines indicate that a rejection is proper only in the "rare instance" where an assertion made by the applicant as to how to use the invention is not credible to one of ordinary skill in the art (pages 296-298 of the guidelines).

Regarding the qualifications for "credibility", the guidelines indicate that a specific assertion of how to use the invention not only creates a presumption of validity, but also is deemed credible "unless (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion" (page 303 of the guidelines, emphasis supplied).

Applicant also points out the discussion in the guidelines with regard to *in vitro* experimental data and the requirement for human clinical data. Specifically, page 306, right column, states that if reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays....almost invariably will be sufficient to establish therapeutic or pharmacological utility for (or how to use) a compound. The same section states that in no case has a Federal court required an applicant to support an assertion of how to use a with data from human clinical trials.

This section of the guidelines further states that primary responsibility for determining the existence of a therapeutic or pharmacological utility for a compound,

composition or method in humans lies with those who are "especially skilled in the art" at the U.S. Food and Drug Administration, not with the U.S. Patent Office.

Summary of the guidelines

Applicant, therefore, summarizes the new guidelines to state the following:

(a) a credible assertion made by the Applicant as to how to use a compound is presumed valid;

(b) the assertion is considered credible unless the underlying logic of the assertion is seriously flawed or the logic is valid but the facts are not consistent with the logic; and

(c) *in vitro* data is invariably sufficient to establish how to use a therapeutic or pharmacological compound so long as a reasonable correlation between the data and the assertions made by applicant can be established.

Under the proper standard, the specification discloses how to use the invention

Applicant submits that (a) an assertion of "how to use" has been made, (b) the logic is not seriously flawed and the facts are consistent with the logic, and (c) that the data presented in the specification is reasonably correlated with the purported assertions. Applying this standard, Applicant addresses each of the issues set forth above regarding the enablement of the invention individually.

The claimed methods for killing target cells and reducing the concentration of target molecules are enabled for mammalian hosts

The Office Action states that the *in vitro* or *in vivo* mouse data does not enable human use. The claims are directed to killing target cells and reducing the concentration of target molecules in a mammalian host. As discussed above, only *in vitro* data is required to show how to use a pharmacological compound in a human. However, the present specification provides *in vivo* mouse data in addition to the *in vitro* data.

Therefore, the mouse data adds further support for use in mammalians than is necessary for patentability.

The specification provides two examples in accordance with the present invention where the methods were applied to mice. Page 23, lines 18-27 of the specification, demonstrates that injection of conjugate into mice previously transfused with anti-FITC antibodies results in a decrease in the numbers of the target cells over the control groups. Page 30, lines 7-16 of the specification, demonstrates the prolongation of heterotopic cardiac grafts in mice treated in accordance with the present invention. In addition to the *in vivo* data, various *in vitro* experiments were performed such as the one showing that the conjugate initiates complemented mediated lysis, page 22, lines 15-22 of the specification.

Therefore, applying the standard for determining whether a specification discloses "how to use" a compound, Applicant asserts that in accordance with the present invention, a conjugate can be administered to a mammalian host wherein an agent is targeted and killed (or eliminated from the bloodstream). The logic is that one moiety of the conjugate targets a selected agent and another moiety of the conjugate binds to an effector agent providing for death or elimination of the selected agent. The facts are consistent with this logic in that supporting data has been presented in the specification as outlined above. The data presented in the specification is reasonably correlated with the purported assertions in that conjugates administered in accordance with the present invention eliminated target cells in one experiment (page 23) and provided for therapeutic selective immunosuppression in another experiment (page 30). Both experiments were performed in mice *in vivo*.

A specification that discloses information on how to make and use the invention must be accepted unless the Patent Office provides sufficient reason to doubt the accuracy of the disclosure. If the Patent Office does present doubt to the accuracy of the disclosure, then such a rejection can be overcome by suitable proofs such as expert declarations confirming the assertions made in the application. In re Marzocchi, 439

F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971). In this case, the Patent Office has questioned the accuracy of the assertions made in the specification by pointing out the discussions in Edgington, *Bio/Technology*, 10:383-389 (1992) (Edgington), and Osband, et al., *Imm. Today*, 11:193-195 (1990) (Osband). Specifically, Edgington is offered as supporting the assertion that *in vitro* data alone does not establish that an agent can be used *in vivo* in humans for the treatment of a disease, and Osband is offered as supporting the assertion that the response of animals to immunotherapy is not predictive of the response in humans.

Regarding Edgington, Applicant submits that this article provides no scientific data, but rather provides unsupported opinions. Since the opinions of Edgington are not supported with scientific data, they cannot rebut the assertions set forth by the Applicant which are supported by *in vitro* and *in vivo* data.

Regardless, Applicant submits that the variable factors brought up by Edgington regarding applying *in vitro* data as a predictor of performance *in vivo* have been considered in the application. Specifically, one skilled in the art would be aware of techniques to humanize antibodies, and the use of rodent antibodies would not be administered in the expectation that they would be effective over a prolonged period of time. However, Applicant points out the guidelines discussed above which state that *in vitro* data is invariable sufficient to establish how to use therapeutic compounds. Furthermore, Applicant does not provide only *in vitro* data, therefore, Edgington is not an issue.

Regarding Osband, page 194, lines 3-5, states that "it will be necessary to develop immunotherapy for humans in humans". Again, similar to Edgington, Osband does not provide scientific data but rather provides unsupported opinions. Furthermore, the proposition that humans be used to prove therapeutic use is not a widely accepted viewpoint.

As discussed above, the viewpoint of the Patent Office is that *in vitro* data is generally sufficient to determine patentability whereas data for use in humans is best

considered by the U.S. Food and Drug Administration, not the U.S. Patent Office. The viewpoint of the Federal courts is that an applicant is not required to provide data from human clinical trials to support a patent. In this case, *in vivo* data is provided in addition to *in vitro* data, therefore, the data is sufficient to meet the standards for patentability.

However, if it is the case that the Patent Office has successfully raised a doubt to the accuracy of the statements asserted in the application by pointing out the viewpoints of Edgington and Osband, Applicant submits herewith "suitable proofs" confirming the assertions made in the application to overcome the rejection in accordance with In re Marzocchi. Specifically, Applicant submits a copy of the Declaration under 37 C.F.R. Section 1.132 previously submitted to the Patent Office in the parent application, Serial No. 08/254,299, mailed on June 5, 1996. This Declaration was not considered in the parent case as the Advisory Action mailed July 2, 1996, in that case stated that the Declaration was not timely submitted.

The Declaration states that "The rodent model is generally accepted in the field as a screen for immunosuppressant drugs," page 2, lines 5 and 6. Page 4, lines 1-3, states, "In my expert opinion, the rodent model supports the continued development of the subject invention for transplants and provides a reasonable degree of confidence of anticipated success in humans." Therefore, this Declaration clearly confirms the assertions that the claimed methods are fully enabled by the specification. Applicant points out that the Declarant, Dr. Jean-Paul Soulillou, is not an inventor, and is a qualified expert as a member of the editorial board of several scientific journals.

Applicant again points out that the standard for enablement is a "reasonable correlation" between the data and the assertions such that one skilled in the art would have a "reasonable" degree of confidence of success in practicing the claimed invention. Therefore, Applicant submits that if, *arguendo,* the Patent Office has raised a doubt to the accuracy of the disclosure, Applicant has met the burden of proof required to refute that doubt by submission of the enclosed Declaration. Therefore, Applicant respectfully requests the Examiner to reconsider and withdraw the rejection.

The *in vivo* data relating to lysis f cells enables killing cells

The Office Action (bridging pages 9 and 10) states that the *in vivo* data showing lysis of normal cells does not indicate that the claimed method would treat diseases. First, Applicant points out that the claims are drawn to killing target cells or reducing the concentration of target molecules.

Regarding the "kind of cells" targeted, Applicant points out that any number of surface proteins can be targeted, and therefore, a variety of cell types ("diseased" or not) can be targeted (page 6, lines 4-22, of the specification). The principal remains the same, the conjugate will target a cell and then cause that cell to be killed or eliminated.

More specifically, regarding the lysis of "normal" cells in treatment, in the case of immunosuppression, the cells targeted to be killed may be considered "normal" in response to a transplant, but for successful treatment, this "normal" response must be modulated. Specifically, a therapeutic benefit can be effected by redirecting a natural antibody response.

Lastly, regarding the statement in the Office Action regarding the lack of therapeutic demonstrative examples, Applicant points out that in addition to the *in vivo* data demonstrating selective cell lysis, Example 5 (pages 29 and 30) shows the prolongation of heterotopic cardiac grafts in mice. Therefore, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

Antibody conjugates are enabled by animal data

Addressing the first full paragraph of page 10 of the Office Action, Applicant submits that the *in vivo* data discussed above utilizes conjugates comprising antibodies. Applying the standard in the guidelines for showing "how to use" a compound, the assertions by Applicant remain the same. Specifically, the logic of how to use the invention is that the antibodies will bind to an effector system to cause elimination of the target cell, and that the *in vivo* data of mice provides a reasonable expectation of success in practicing the invention in humans.

To question the assertions made in the application, the Office Action points to Waldmann, *Science*, 252:1657-1662 (1991) (Waldmann) and Harris, et al., *TIBTECH*, 11:42-44 (1993) (Harris). Specifically, Waldmann is offered to support the assertion that the therapeutic use of antibody treatment is unpredictable from *in vitro* or *in vivo* animal data alone. Waldmann also states that effectiveness of murine antibodies is limited due to immune responses, and that even human antibodies can be similarly limited by virtue of their idiotypic elements. Harris is offered to support the assertion that there is widespread acceptance that there is little future for the use of rodent mAbs for *in vivo* human therapy.

First, Applicants point out that Harris and Waldmann are not in hindsight of the present application. Specifically, one skilled in the art would expect that given the present application, containing multiple *in vitro* and *in vivo* experiments showing positive data, one skilled in the art could practice the claimed invention despite the opinions proffered by Harris and Waldmann.

Furthermore, Applicant points out that Waldmann states that "humanized antibodies" are less immunogenic than their murine counterparts except in some cases. Therefore, Waldmann does not state that humanized antibodies cannot be useful to provide some beneficial effect.

Waldmann also clearly states that "one solution to the problems of immunogenicity....is to produce human monoclonal antibodies", page 1659, first sentence of last paragraph, left column. Page 17, lines 9-15, of the specification shows that human antibodies were purified from human pooled plasma. Therefore, the specification does teach how to enhance the efficacy of the antibodies. However, it is the Applicant's position that even rodent antibodies would provide a measurable therapeutic effect.

If it is the case that the Patent Office has successfully raised a doubt to the accuracy of the disclosure, Applicant has submitted herewith acceptable proof to rebut the rejection in accordance with In re Marzocchi discussed above. Specifically,

Applicant again points to the enclosed copy of the Declaration under 37 C.F.R. Section 1.132 previously submitted to the Patent Office in the parent application, Serial No. 08/254,299, mailed on June 5, 1996.

The last paragraph of page 3 of the Declaration states that "A single dose of the (rodent) monoclonal antibody is not likely to induce an immune response....Further doses should also be permissible". The Declaration also states in this paragraph that "Under a variety of conditions, such (rodent) monoclonal antibodies are useful." Moreover, the Declaration states "the initial few days ....are of the greatest concern". Therefore, this Declaration confirms the assertions that the antibody conjugates are enabled and refutes the doubts which, *arguendo*, may have been raised by Waldmann and Harris regarding the use of antibodies in accordance with the claimed invention. Applicant, therefore, respectfully requests the Examiner to reconsider and withdraw the rejection.

IL-2 or other cytokines as a ligand are enabled for killing target cells

Addressing the Office Action beginning at the bottom of page 10, Applicant understands this rejection to be primarily directed at the issue of whether normal cells are inactivated while inactivating the target cells. Again, Applicant points out that the claims are directed at killing target cells or reducing the concentration of target molecules. The specification supports these claims.

The specification provides *in vivo* data demonstrating that a dosage can be administered which provides for a therapeutic effect. Specifically, the data shows that cells are lysed and that cardiac grafts in mice can be prolonged. Concerning the use of IL-2, normal T cells can be the target cell. In referring to normal T cells, in the case of organ transplants, one wishes to diminish the cytotoxicity of the T cell response. Similarly, one may wish to destroy normal cells having a particular cytokine receptor. Therefore, the present invention provides a method of ablating cells, which are in effect normal or abnormal, but in either case are undesirable. One skilled in the art would modulate the treatment such that treatment would cease when the desired effects were

obtained. Applicant, therefore, respectfully requests the Examiner to reconsider and withdraw the rejection.

Methods utilizing the α-gal antigen are enabled

Addressing the Office Action at the first full paragraph of page 11, Borrebaeck, et al., *Imm. Today*, 14:477-479 (1993) (Borrebaeck) is offered in the Office Action to support the assertion that the preformed antibodies (endogenous antibodies) do not act as an immunologic effector system upon binding to an exogenously administered agent, but rather result in the removal of the agent thus preventing the agent from reaching the appropriate target cell.

Applicant points out that Borrebaeck states that mouse antibodies are rapidly eliminated because of the presence of the α-gal epitope, but Borrebaeck also states that the amount of glycosylation varies with some of the antibodies being "particularly heavily glycosylated" (page 477, column 2). Therefore, Borrebaeck suggests that by reducing the degree of glycosylation, this issue may be obviated. Regardless, these antibodies are not analogous to the conjugates of the subject invention, where only a single α-gal epitope would be involved.

However, if a doubt has been raised as to the accuracy of the assertions in the specification, Applicants again point to the enclosed Declaration to refute this rejection. Specifically, third page, second full paragraph, states that "A large number of rodent monoclonal antibodies have been administered to humans and in many cases with positive effects.....the α-gal epitope has not been reported to be a problem." This Declaration clearly refutes Borrebaeck and confirms the efficacy of the claimed methods

as demonstrated in the examples of the specification. Applicant, therefore, respectfully requests the Examiner to reconsider and withdraw the rejection.

Methods utilizing endogenous antibodies to α-gal are enabled

Borrebaeck is also offered to support the assertion that anti-a-gal endogenous antibodies are not found in mammals, but only in humans and old world monkeys. Applicant concurs, anti-α-gal antibodies are only present in mammals which do not have α-gal. However, since the claims are directed to those of ordinary skill in the art, it would be obvious that the claims utilizing these antibodies would be similarly limited. It is well established that the claims are directed to the operative embodiments of the claimed subject matter. The Examiner is therefore respectfully requested to withdraw this rejection.

Dosages for the conjugate and the endogenous antibodies are provided

Applicant discloses specific dosages in mice which provide therapeutic effects. Applicant also demonstrates two different concentrations and their effect on reduction of cell numbers in mice in Figure 6. This data could be correlated with an effective dosage for humans by one skilled in the art. Applicant submits that it is well within the skill level in the art to correlate the dosage administered mice to the appropriate dosage to administer to other mammals. For example, the specification demonstrates that where cardiac grafts were prolonged in mice, 50 mg/Kg of conjugate were administered (page 30, line 10. The specification, at page 30, lines 3-6, also provide data showing doses where the conjugate is not toxic. Therefore, the specification provides enabling data for one skilled in the art to administer the conjugate to a mammalian host to kill cells or reduce the concentration of target molecules. The Examiner is, therefore, respectfully requested to withdraw this rejection.

Rejections Under 35 U.S.C. Section 112, Second Paragraph

Claim 6 was rejected under 35 U.S.C. Section 112, second paragraph, as being indefinite in the recitation of "low molecular weight binding protein". Applicant

traverses. Claim 6 has been amended to define low molecular weight binding proteins as those having a molecular weight of more than 100 and less than about 5000 daltons. Support is found on page 6, lines 23-25. Applicant also points out that Claim 6 has been amended to replace "selective moiety" with "moiety specific for a surface protein" in accordance with page 6, lines 23 and 24. Applicant, therefore, requests that the rejection be withdrawn.

Rejections Under 35 U.S.C. Section 102--Claims 1, 5 and 6

Claims 1, 5 and 6 have been rejected under 35 U.S.C. Section 102 as anticipated by U.S. Patent No. 4,676,980 to Segal et al., (Segal) as evidenced by Roitt, Essential Immunol., Blackwell Sci. Press, pp. 48 and 49 (1988) (Roitt) and Rosen, et al., Dictionary of Immunology, Stockon Press, p. 140 (1989) (Rosen). Applicant traverses.

A review of the publications

Segal discloses heteroantibodies defined as two or more cross-linked, dissimilar antibodies. Roitt discloses that the T-cell receptor is a heterodimer which is not the product of immunoglobulin genes. Rosen defines a ligand as a chemical group or molecule bound to another chemical group or molecule. In summary, the publications are offered as supporting the assertion that the claimed invention includes heteroantibodies as disclosed in Segal since the moiety for a ligand as recited in the claims could be interpreted as being an antibody.

The claimed subject matter

In an effort to expedite prosecution, Claim 1 has been amended to clarify that the moiety specific for a surface protein is not an antibody, as amended in the grandparent case Serial No. 07,690,530 in the Amendment mailed September 21, 1993. Applicant requests that this amendment be made without prejudice. In the grandparent case, the Advisory Action mailed October 6, 1993, stated that this amendment to Claim 1

overcame the rejection under Segal. Therefore, in view of the present amendment and the file history of the grandparent application, Applicant respectfully requests the Examiner to withdraw this rejection.

Rejections Under 35 U.S.C. Section 102, Claims 1-6 and 12

Claims 1-6 and 12 have been rejected under 35 U.S.C. Section 102 as anticipated by EP 0510949 by Pouletty (Pouletty). Applicant traverses.

The requirements to find anticipation

To anticipate the invention, the reference must enclose within its four corners, each and every claimed element. It is also required that the reference be enabling to one skilled in the art.

Pouletty is essentially the same disclosure as Serial No. 07/690,530 filed April 23, 1991, the grandparent application to the present application. Therefore, if it is the Examiner's position that Pouletty anticipates, then it must be the Examiner's position that the grandparent application is enabling for the present invention. Since the grandparent was disclosed before Pouletty, then Pouletty is removed as a reference.

The present application has the priority date of the grandparent application

Applicant addresses the issues relating to the proper priority date in the order presented in the Office Action at page 13.

Concerning Claim 2, although the term "xenoantigen" is not used in the grandparent application, a large number of xenoantigens are described in that application beginning at page 4, line 36 and continuing to page 5, line 3. To clarify the consistency between the grandparent application and the present application, the term "xenoantigen" has been replaced with "antigen foreign to the host". Support for this amendment is found on page 8, lines 1-5 of the present application, and page 5, line 1 of the

grandparent application. Applicant, therefore, requests the Examiner to withdraw the rejection of Claim 2.

Regarding Claim 6, page 4 of the grandparent application provides a plethora of possible moieties that bind to the target cell receptors including those which bind to infectious agents, LPS, or other pathogenic cellular markers. These molecules vary in weight and inherently include low molecular weight binding molecules. Applicant, therefore, requests the Examiner to reconsider and withdraw the rejection of Claim 6.

Regarding the "SEB" or "Mis" (amended as "MIs" not "MLs" as stated in the Office Action) of Claim 3, page 5, line 6 of the grandparent application recites, "SEC1, SEA, SBB, ExFT, TSST1, MIs". Line 6, line 8 of the present application recites "SEC1, SEA, SEB, ExFT, TSST1, MIs". It is clear that given the context in which it is recited, "SBB" of the grandparent application was intended to be "SEB", and was therefore an obvious typographical error which has since been corrected. Applicant, therefore, requests the Examiner to withdraw the rejection to Claim 3.

Regarding the "proviso (b)" of Claim 1, page 4, line 7, of the grandparent application verbatim recites that this moiety can be a "ligand". Therefore, Applicant requests that the rejection to Claim 1 be withdrawn.

Regarding the method of Claim 12 using antibody against any T cells, Applicant points to page 4, line 13 of the grandparent application which recites molecules which bind to T cells. Applicant, therefore, respectfully requests that the rejection to Claim 12 be withdrawn.

As Applicant has shown that the present application is enabled as of the filing date of the grandparent application, the present application is entitled to the April 23, 1991, filing date. Moreover, since Pouletty was filed one year after, on April 23, 1992, Pouletty cannot anticipate the present application.

Rejections Under 35 U.S.C. Section 103--Claims 1 and 6

Claims 1 and 6 are rejected under 35 U.S.C. Section 103 as unpatentable over Ochi, et al., *Eur. J. Immunol.*, 17:1645-1648 (1987) (Ochi) in view of Roitt. The rejection set forth is identical to the one set forth in paragraph 35, pages 17 and 18 of the Office Action mailed June 27, 1995, in the parent application, Serial No. 08/254,299. More specifically, the rejection states that Ochi discloses a conjugate consisting of keyhole limpet hemoxyanin (KLH) covalently linked to an anti-id monoclonal antibody that binds to B cell lymphoma. The rejection further states that KLH binds to a T cell, and that Roitt establishes T cell binding to occur via a receptor. Applicant traverses.

Claims 1 and 6

Claims 1 and 6 require that a moiety and a selective moiety be joined to form a killing complex....whereby when said conjugate is bound to said target cell and said effector agent, said cell is killed. For clarification, Claim 1 has been amended to state that the conjugate is bound to both of said target cell and effector agent.

Ochi

In contrast, Ochi forms an anti-Id-KLH complex that does not function as a killing complex which binds to both the target cell and the effector agent to kill the cell. Rather, the anti-Id-KLH complex first binds to the target cell (limited to B cells) by way of the Id determinant of the surface immunoglobulin of the B cell lymphoma (line 6 of the abstract). But, the complex does not then bind to an effector agent in the form of a killing complex. Instead, as detailed on page 1647 of Ochi, lines 7-15 of the "Discussion" section, Ochi discloses that the anti-Id-KLH complex is internalized by the B cell lymphoma. The KLH is then processed and a portion is externalized for recognition by T cells (limited to KLH specific T helper cells). Therefore, Ochi discloses that KLH is presented by the target cell in the context of an MHC to a T helper

cell. The form in which the anti-Id portion of the original conjugate is in at this point is not disclosed.

Therefore, while Ochi should be successfully distinguished on the grounds that Ochi has no *in vivo* data, Ochi may be further distinguished for disclosing a method that does not form a conjugate which is in itself a killing complex and which binds to both the target molecule and the effector agent. Ochi requires that the conjugate be endocytosed, digested, and a fragment presented at the surface in conjunction with an MHC. Roitt does not cure the deficiencies of Ochi. Roitt merely describes the T cell receptor and it's function.

Ochi and Roitt do not disclose or suggest all of the claimed elements, therefore, they do not provide a reasonable expectation of success in combining the claimed elements without the hindsight of the present invention. For these reasons, Ochi and Roitt would not lead one skilled in the art to find the present invention obvious.

Moreover, Applicant points out that the argument submitted above was previously submitted in the Amendment mailed September 26, 1995, in the parent application in response to the same rejection. Applicant also points out that in the next Office Action in that application, mailed February 6, 1996, all of the rejections under 35 U.S.C. 103 over Ochi were withdrawn. Applicant, therefore, respectfully requests that in accordance with the above remarks and the history of this case, the Examiner reconsider and withdraw the rejection.

Rejections Under 35 U.S.C. Section 103--Claims 2 and 3

Claims 2 and 3 have been rejected under 35 U.S.C. Section 103 as unpatentable over Ochi and Roitt, in view of Dohlsten, et al., *Immunol.*, 71:96-100 (1990) (Dohlsten) and Pullen, et al., *Cell*, 61:1365-1374 (1990) (Pullen). The rejection set forth is similar to the one set forth in paragraph 36, pages 18-20 of the Office Action mailed June 27, 1995, in the parent application, Serial No. 08/254,299. Specifically, the rejection states

that Pullen discloses that staphylococcal enterotoxins were known in the art as superantigens and that Dohlsten discloses that SEA, SEB or SEC1 could mediate T cell killing of target cells. Therefore, the rejection concludes it would have been obvious to combine the superantigens of Dohlsten and Pullen with the method of Ochi to arrive at the present invention. Applicant traverses.

Since the combination of Ochi and Roitt have already been shown to be unsuggestive of the subject invention, and their inadequacies are not corrected by Dohlsten and Pullen, it should follow that Claims 2 and 3 are also patentable. If one followed Ochi, the superantigen would merely provide a fragment which when bound to an MHC would be recognized by T helper cells. Whether the superantigens have fragments which provide for strong binding to MHCs and the resulting complex has strong binding to endogenous helper cells, is all a matter of conjecture.

Applicant points out that the above argument obviated the rejection over Ochi, Roitt, Dohlsten and Pullen in the parent application. Therefore, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

Rejections Under 35 U.S.C. Section 103--Claim 4

Claim 4 has been rejected under 35 U.S.C. Section 103 over Pouletty in view of the "prior art disclosed in the specification (page 9, first complete paragraph)". This rejection was presented in the parent application, where the references were on page 9. In the present application, these references are on page 8, and Applicant assumes that to these references the Examiner now refers. Specifically, Applicant understands this rejection to state that while the α-gal epitope is not specifically disclosed in either the grandparent application or Pouletty (they are substantially the same), endogenous antibodies are disclosed, and it is well known in the art that the body naturally produces antibodies to α-gal. Among the references supporting this assertion are Galili, et al., *J. Exp. Med.*, 162:573-582 (1985) (Galili-1985) and Galili, et al., *PNAS USA*, 84:1369-

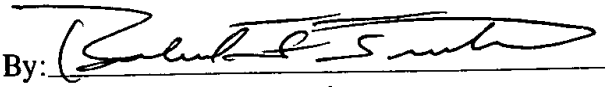
1373 (1987) (Galili-1987). Therefore, the rejection concludes that it would have been obvious to combine the disclosure of Galili-1985 and Galili-1987 that α-gal antibodies are endogenous with the disclosure of Pouletty which describes the use of endogenous antibodies, to arrive at Claim 4. Applicant traverses.

Applicant submits that since α-gal antibodies were known to be endogenous antibodies at the time of the filing of the grandparent application, (the supporting publications are dated 1985 and 1987), and because endogenous antibodies are described in the grandparent application at page 4, lines 24-30, the present application is entitled to the priority date of the grandparent application and Pouletty cannot be considered as prior art. Applicant, therefore, respectfully requests the Examiner to withdraw the rejection.

In view of the above amendments and remarks and the accompanying Declaration, the Examiner is respectfully requested to withdraw the rejections and allow Claims 1-13. Applicant believes the claims stand in condition for allowance. Applicant earnestly solicits such allowance.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP

By: 

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APPENDIX--CLAIMS AS PENDING

1. (Amended) A method for killing a target cell in a mammalian host comprising said target cell and an endogenous cytotoxic effector system comprising a least one effector agent, said method comprising:

introducing a conjugate into said host in sufficient amount to kill the target cells, wherein said conjugate is characterized by comprising a moiety other than an antibody specific for a surface protein joined to a selective moiety capable of binding to said effector system to form a cell killing complex, with the proviso that when said selective moiety binds to a T-cell, (a) it binds to the T-cell receptor and (b) said moiety specific for a surface protein is a ligand; wherein said effector system comprises (1) antibodies specific for said selective moiety and an antibody dependent cytotoxic system comprising at least one effector agent or (2) a T-cell, whereby when said conjugate is bound to both of said target cell and said effector agent, said cell is killed.

2. (Amended) A method according to Claim 1, wherein said selective moiety is a blood group antigen, [xenoantigen] an antigen foreign to said mammalian host to which antibodies are present in said mammalian host or a superantigen.

3. (Amended) A method according to Claim 2, wherein said selective moiety is a superantigen selected from the group consisting of SEC1, SEA, SEB, ExFT, TSST1, [Mis] MIs, or minor histocompatibility antigen.

4. A method according to Claim 2, wherein said selective moiety binds to anti-α-gal antibodies.

5. A method according to Claim 1, wherein said selective moiety binds to a cytotoxic T-cell.

6. (Amended) A method according to Claim 1, wherein said [selective] moiety specific for a surface protein is a low molecular weight binding molecule, wherein said molecular weight is more than 100 and less than about 5000 daltons.

7. A method according to Claim 1, wherein said moiety for said surface protein is a ligand for a cytokine surface membrane protein receptor of said target cell.

8. A method according to Claim [6] 7, wherein said ligand is IL-2.

9. A method for killing a target cell in a mammalian host comprising said target cell, said method comprising:

introducing a conjugate into said host comprising an endogenous cytotoxic effector system, comprising at least one effector agent, capable of killing said target cell, wherein said conjugate is characterized by comprising a cytokine which binds to a surface membrane receptor on said target cell joined to a selective moiety which binds to said effector agent to form a cell killing complex, wherein said selective moiety is a blood group antigen or at least a portion of a protein vaccine and said effector agent comprises an immunoglobulin, whereby when said conjugate is bound to said target cell and said effector agent, said cell is killed.

10. (Amended) A method according to Claim [8] 9, wherein said cytokine is a interleukin.

11. (Amended) A method according to Claim [9] 10, wherein said interleukin is IL-2

12. A method for killing a target cell in a mammalian host comprising said target cell and an endogenous cytotoxic effector system comprising cytotoxic T cells, antibody dependent cytotoxic cells, and complement, said method comprising:
introducing into said host a conjugate, comprising an immunoglobulin fragment specific for a surface membrane of a T cell and a ligand to which antibodies are endogenously present in said mammalian host, in sufficient amount to substantially kill a target T cell population, wherein said cell is killed.

13. A method for reducing the concentration of a soluble target molecule in the blood stream of a mammalian host, said method comprising:
introducing a conjugate into said host comprising an endogenous cytotoxic effector system, said conjugate comprising a selective moiety having a specific affinity for a soluble blood component target molecule and a ligand for an endogenous immunoglobulin, wherein said endogenous cytotoxic effector system comprises an immunoglobulin specific for said ligand, whereby when said conjugate is bound to said target molecule and said effector agent, said target molecule is eliminated from said blood stream.